

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
20 April 2006 (20.04.2006)

PCT

(10) International Publication Number
WO 2006/041365 A1

(51) International Patent Classification⁷: **A61L 27/10**,
A61K 47/02, A61L 27/58

(21) International Application Number:
PCT/SE2005/001304

(22) International Filing Date:
9 September 2005 (09.09.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0402196-0 10 September 2004 (10.09.2004) SE

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: RESORBABLE CERAMIC COMPOSITIONS

(57) Abstract: The present invention relates to ceramic precursor compositions and chemically bonded ceramic (CBC) materials, especially Ca-based, and a composite biomaterial suitable for orthopaedic applications. The CBC-system includes a binding phase (chemical cement) and additional phases with specified chemistry imparting to the biomaterial the ability of initial strength followed by interaction with the body tissue including body liquid, to form a resorbable or partly resorbable biomaterial. The ceramic precursor composition comprises at least one silicate with Ca as the main cation with a resorption rate less or equal to that of the bone in-growth rate. Said silicate will form the binding phase of the cured material. The invention also relates to implants and surface coated devices. The cured material exhibits a compressive strength exceeding 100 MPa.

WO 2006/041365 A1

RESORBABLE CERAMIC COMPOSITIONS

Field of the invention

The present invention relates to ceramic precursor compositions and chemically
5 bonded ceramic (CBC) materials, especially Ca-based, and a composite biomaterial
suitable for orthopaedic applications. The CBC-system includes a binding phase
(chemical cement) and additional phases with specified chemistry imparting to the
biomaterial the ability of initial strength followed by interaction with the body tissue
10 including body liquid, to form a resorbable or partly resorbable biomaterial. The
invention also relates to a cured ceramic material, implants and surface coated de-
vices.

Background

For materials to be used as bone void fillers, which have to interact with human
15 tissue, it is advantageous to make the biomaterials as biocompatible and bioactive
as possible. This can be achieved principally by at least two routes – developing
stable biocompatible materials or resorbable materials allowing new bone tissue to
substitute the biomaterial. The first route to make more stable materials, e.g.
PMMA-based materials or Ca-aluminate-based materials, is especially suitable for
20 osteoporotic clinical situations. For active or young patients a resorbable material,
e.g. soluble glasses and phosphate-based materials, may be the most attractive
route, where interaction with living tissue is more pronounced. It is well known that
calcium aluminates and calcium silicates can have a considerably higher compres-
sive strength than those of the present resorbable materials (in the order of 100
25 MPa).

The traditional resorbable phases contain oxides of Ca and P (or S). Ca-phosphates
and or Ca-sulphates and glass containing CaO, P₂O₅, SiO₂ and Na₂O are typical
representatives for this low-mechanical strength category of bioelements.

30

In EP 1 123 081 B1 and EP 0 555 807 Ca-silicate is mentioned as an additional
phase for drug uses (less than 10%) and for bone substitute products as an addi-
tional divalent compound. Regarding biocompatibility of Ca-silicate materials, work
have been done on the endodontic treatment material Proroot or MTA and on Wol-
35 lastonite materials. See J. Saidon, et al, "Cells and tissue reactions to mineral triox-

ide aggregate and Portland cement", Oral surgery medicine pathology, April (2003) 483-489. Wollastonite is an established biomaterial in the form of sintered ceramic pieces. A survey of bone cements is found in S. M. Kenny and M. Buggy, "Bone cements and fillers: A Review", Journal of Materials Science: Materials in Medicine, 14
5 (2003) 923-938.

In view of the prior art materials for use, particularly in, bone void filling, there is a need for a biocompatible material exhibiting resorbability and sufficiently high strength, and thus load-bearing capacity, shortly after application, as well as later on.
10

Brief description of the invention

To fulfil the above-mentioned needs, the present invention provides ceramic precursor compositions and cured products exhibiting the above-mentioned features.

15 The object of the present invention is to provide ceramic precursor compositions based on chemically bonded ceramics as main phase(s), which when cured, provides a sufficiently high-strength (compressive strength 100-150 MPa) ceramic product. Said strength is achieved shortly after application of a slurry, paste or semi-hardened mixture of the ceramic precursor composition in a defective site. The
20 initial high strength makes load-bearing possible for the defective site during the resorption stage, where new bone tissue takes over the load-bearing capacity.

During curing, the binding phase(s) according to the present invention consumes or takes up a great deal of water, whereby the cured ceramic product exhibits a low
25 residual porosity, which contributes to the high strength.

According to a first aspect, there is provided a ceramic precursor composition comprising at least one particulate Ca-silicate, and possibly other particulate Ca-compounds selected from phosphates, carbonates, sulphates and combinations
30 thereof, having calcium as the major cation. Said compound(s) will form the main binding phase(s) in the cured material. The ceramic precursor composition is defined in claim 1.

In another embodiment, said ceramic precursor compositions also include a second binding phase (e.g. high-strength Ca-aluminates) contributing to the high compressive strength, both initially and later on.

- 5 The constituents of the ceramic precursor composition are particulate matter, unless stated otherwise. The percentages given for the precursor composition, as well as for the cured ceramic material, represent weight-%, unless stated otherwise.

10 According to second aspect, there is provided a cured ceramic material, which is obtained by mixing the precursor composition and a curing liquid, i.e. water. The cured ceramic material is defined in claim 11.

15 According to third aspect, there is provided a medical implant which comprises the non-cured ceramic precursor composition and/or the cured ceramic material according to the invention. The medical implant is defined in claim 27. Said medical implant may be used as a carrier material for drug delivery. Said use is defined in claim 28.

20 According to fourth aspect, there is provided a surface coated device selected from the group consisting of an artificial orthopaedic device, a spinal implant, a joint implant, an attachment element, a bone nail, a bone screw, and a bone reinforcement plate, which device or substrate is coated with the non-cured ceramic precursor and/or the cured ceramic material according to the invention. The coated device or surface is defined in claim 29.

25 The major advantages of the present invention precursor composition, cured material and product, when inserted or injected into a body, is that they have a high resorbability, such that a high in-growth rate of a bone is achieved. The resorption rate is less or equal to that of the bone in-growth rate. This is important to keep the
30 loading capacity during the whole healing period.

The compressive strength level obtained with the cured material according to the present invention is within the interval 100-150 MPa – to be compared with that of other resorbable biomaterials with a compressive strength in the interval 20-60
35 MPa.

The strength level for biomaterials according to the present invention is at least equal to that of stable biomaterials for bone void filler applications, such as PMMA – based materials, which do not exhibit the same degree of resorbability.

5

The ceramic material according to the invention have the advantages compared to prior art systems/materials, such as bioglasses, glass ionomer cements and pure Ca-phosphate-based systems or monomer-based filling materials, that it maintains its bioactivity, that it has improved initial strength and that it is dimensionally stable – i.e. exhibits a limited expansion instead of shrinking like known resorbable materials, which benefits the contact with the tissue.

10

The ceramic materials according to the invention have been especially developed for biomaterials used as bone void filler materials for orthopaedic applications, but can also be used as resorbable filler materials-within odontology, including endodontics.

15

Detailed description of the invention

The present invention deals with bioactive ceramics based on resorbable ceramics. However, in addition to this, the present invention also deals in detail with the time aspects of strength development and the level of strength obtained. Accordingly, the present invention aims at providing materials, preferably biomaterials, having early and maintained strength, which with time dissolves and interacts with the body system to yield new tissue.

20

In a basic form, the ceramic precursor composition according to the invention comprises main binding phase(s) of chemically bonded ceramics, preferably Ca-silicates, with Ca as the main cation. The binding phase(s) preferably comprises one or more of the following phases:

25

$C3S = 3(CaO)(SiO_2)$, $C2S = 2(CaO)(SiO_2)$, and $CS = (CaO)(SiO_2)$. The main binding phase(s) of the ceramic precursor composition comprises more than 50 weight-% of at least one Ca-silicate. In a further preferred embodiment, the main binding phase comprises $3CaO \cdot SiO_2$. In a preferred embodiment, the main binding phase(s) of the cured ceramic material comprises hydrates of $3CaO \cdot SiO_2$. Said main binding phase(s) may also comprise phosphates, carbonates, sulphates of calcium, and

30

combinations thereof. The remainder, if any, is constituted by additives such as inert phase and/or additives that make a material radiopaque.

5 The use of soluble chemically bonded ceramic based on $3\text{CaO}\cdot\text{SiO}_2$ is preferred, since it offers both resorbability, and a high initial consumption or up-take of water that reduces the porosity, whereby a high strength is achieved early after the application of the ceramic precursor composition mixed with a curing liquid.

10 As second binding phase(s), the ceramic precursor composition may further comprise a Ca-compound based on phosphate and/or sulphates in an amount of less than 20 weight-% of the main binding phase(s), preferably an amount of 5-10 weight-%. Said second binding phase may comprise a soluble glass, e.g. a phosphorous-containing glass, apatite-based materials, preferably a soluble CaH-phosphate.

15 The ceramic precursor composition may comprise additives conferring high radiopacity, e.g. sulphates such as Ba-sulphate, and other very slowly dissolving inorganic or inert mineral phases. Highly radio-opaque oxides, such as zirconium oxide, are preferred. These inert phases preferably comprises a Ca-silicate-based mineral or Ca-silicate glass. These glasses can preferably contain fluorine and phosphorus
20 to yield fluoride and phosphate ions, which contribute to fluoroapatite formation. Said additives can be included in the composition in the form of glass particles, fibres, whiskers and/or platelets, in concentrations below 20 weight-% of the total composition, more preferably 5-15 weight-%, and most preferably 8-12 weight-%.

25 The ceramic precursor composition may further comprise particles of hydrated chemically bonded ceramics of the same or similar composition as that of the main binding phase(s) in an amount less than 40 weight-%, preferably 10-30 weight-%. This improves the homogeneity of the microstructure and enhances the binding between reacting chemically bonded ceramics and the filler material in the early stage
30 of curing.

In order to further enhance early strength properties, additives may be included which improve initial closure of pores in the ceramic material by pure water uptake, e.g. from the semi-hydrate $\text{CaSO}_4\cdot\frac{1}{2}\text{H}_2\text{O}$ to gypsum ($\text{CaSO}_4\cdot 2\text{H}_2\text{O}$). To solidify
35 the total ceramic product initially, a combination of phosphoric acid and zinc

oxide-forming Zn-phosphate is added. These phases will not contribute to the medium time or long-term properties, only enhance the initial pore closure and initial strength.

5 The initial strength up to a few hours after initialisation of the curing reaction may be further increased by addition of a polyacrylic (PA)-based material. When prior art glass ionomer cements (with PA-additives) are used as biomaterials, one major concern is the low pH and the low chemical stability of secondary phases. However, in the ceramic precursor compositions according to the present invention pure PA acid
10 is used only in a low concentration, less than 8 weight-%, preferably less than 5 weight-% and more preferably 2-3 weight-%, and thus the acid works as an agent reducing the pH in early stages from a pH higher than 11-12 for the initially highly basic silicate and aluminate compounds, to a pH less than 10 within 60 minutes, preferably within 30 minutes in the mixture of the ceramic precursor composition
15 and water.

In order to improve the long-term mechanical strength, high-strength stable additives based on other chemically bonded ceramics, preferably Ca-aluminates, forming hydrates in the cured material, are included in the ceramic precursor composition
20 in an amount less than 40 weight-%, preferably 5-30 weight-%.

The viscosity of the ceramic material prior to curing can be controlled within a wide range, upon initial mixing of the powdered material and the hydration liquid, from moist granules to an injectable slurry. However it is preferable to decrease the water-to-cement (w/c) ratio as much as possible in order to obtain the appropriate viscosity
25 for any given application. The w/c ratio should be less than 0.55, more preferably within the interval of 0.35-0.45. For orthopaedic applications the use of a somewhat higher w/c ratio than that of dental filling materials is possible and desirable to ensure an easily injectable biomaterial.

30 The materials also show slow disintegration rate in water and body liquid when inserted into a body, i.e. that > 95% of the inserted mass is intact after a setting time of 5 minutes, more preferably after a setting time of 10 minutes. This is beneficial since it is important to allow the material to have time for setting without being too
35 much mixed with the surrounding liquid. The setting time is in the interval of 5-12

minutes. The time for defined partial and complete disintegration can be varied within the interval of some months up to a few years.

The cured ceramic material exhibits a compressive strength exceeding 100 MPa. It has a compressive strength within 24 hours of at least 40 MPa, preferably more than 50 MPa within 1 h and more than 90 MPa within 24 h. The compressive strength exceeds 120 MPa after more than 7 days.

After more than 7 days after curing, the cured ceramic material exhibits a K_{IC} -value exceeding $0.5 \text{ MPam}^{1/2}$, preferably exceeding $0.7 \text{ MPam}^{1/2}$, and more preferably exceeding $1.0 \text{ MPam}^{1/2}$.

The dimensional change of the material during curing is less than 0.3 linear %, and/or exhibits an expansion pressure of less than 5 MPa, preferably less than 3 MPa.

The cured ceramic product according to the present invention, when inserted into a body, has a resorption rate that is less or equal to that of the bone in-growth rate. More than 60 weight-% of the material is dissolved within 3 years, preferably more than 50 weight-% within 2 years, and more preferably more than 40 weight-% within 12 months.

The term "bioelement" as used herein, means all types of ceramic or coated objects intended for insertion into a body, such as medical implants including carrier material for drug delivery, and particularly orthopaedic implants. The ceramic precursor composition according to the invention, mixed with a curing liquid, may also be inserted as a slurry, paste or putty, which after curing, forms said bioelement.

Example

An animal model was used to study the resorption rate for bone cement formulations containing calcium silicate as main binding phase(s).

Description of raw materials

The raw materials used were: tricalciumsilicate(C3S), dicalciumsilicate (C2S), monocalciumsilicate (CS) (Nycomineral), mono-calcium aluminate (CA), calcium-

sulphate-semi-hydrate (Merck), tricalciumphosphate (Merck), dicalciumphosphate (Merck), apatite (Merck) and Norian (Syntes Stratec). The C3S, C2S and CA powders were synthesised in-house.

5 *Description of materials*

A number of different powder formulations, that were prepared from the raw materials as mentioned above, are presented in Table 1:1.

Table. 1:1. Composition of the tested formulations in vol.%.

Formulation number	Tricalcium silicate	Dicalcium silicate	Mono calcium silicate	Mono calcium aluminate	Calcium sulphate	Tricalcium phosphate	Dicalcium phosphate	Apatite
1	100							
2		100						
3	70		15		15			
4	70				15	15		
5	70							30
6	70						30	
7	70					30		
8	70				30			
9	60	20				20		
10	60			20	20			
11	75			25				
12	80 (20% hydrated)			20				

10

Description of tests

The powder formulations were mixed with water and a hardening accelerator (30 wt.% CaCl_2) to a calciumsilicate/water ratio of 0.4 using a mixing machine (Rotomix 3MESPE) and plastic jars. Mixing the water and powder yielded an injectable paste.

- 15 The pastes were evaluated with respect to pH change and strength development (measured as compressive strength) over time. The samples submitted to compressive strength testing were stored in simulated body fluid (changed every third day) and subsequently measured after 1h, 24h, 7days, 30 days, 3 months and 12 months. The samples submitted to pH testing were stored in simulated body liquid
- 20 for 5 minutes, 30 minutes, 24 h, 7 days and 30 days. To some of the formulations (Formulations 1-2, 5-6 and 10-11) 2 wt-% of PA-acid was added. The pH change over time was detected.

Each paste was also inserted into an animal model. Bilateral defects were created in the distal femur of skeletally-mature female goats. The medial femoral condyle was exposed and a 10 mm diameter transverse defect was created from the medial cortex to the lateral cortical wall. The graft was placed in this defect site. Each formulation was tested in six sites. The animals were sacrificed after 52 weeks. The medial condyle was submitted to undecalcified histology. The samples were dehydrated, embedded in methyl methacrylate, sectioned in the coronal plane and ground to 20 micrometer thickness. Histomorphometry was conducted to measure bone-to-defect area, graft-to-defect ratio, and bone-to-graft ratio.

Results

The results from the strength test and the results from the resorption study is presented in the Tables 1:2 and 1:3. In the strength test, a commercial calcium phosphate cement was also tested (Norian) as a comparative ceramic. The pH shifted quickly from the initial interval of 11-12 for all formulations according to the invention to less than 10 after 30 minutes and less than 9 after 1h. For samples including the addition of PA-acid, the pH change towards neutral was even quicker. The steady-state pH was higher than neutral.

Table 1:2. The compressive strength development over time for the tested formulations (MPa).

Formulation number	1h	24h	7 days	30 days	3 months	12 months
1	60	100	150	150	150	150
2	40	85	110	130	130	130
3	50	100	110	110	90	90
4	50	90	100	110	80	80
5	45	90	90	120	120	120
6	50	95	100	125	125	125
7	55	100	120	125	130	130
8	40	70	90	100	90	70
9	55	100	110	130	130	130
10	60	100	120	130	130	130
11	70	105	130	130	130	130
12	60	100	130	130	130	130
Norian (comparative)	20	40	40	40	40	40

Table 1:3 Percentage of bone and graft material in defect site after 12 months

Formulation number	% Bone	% Graft
1	30	50
2	20	66
3	40	40
4	40	35
5	20	55
6	30	35
7	35	35
8	50	35
9	30	40
10	40	50
11	35	63
12	30	60

- 5 The results show that all formulations resorb over time and that the maximum strength but slowest resorption rate is achieved when using only calcium silicate as bone graft material.

CLAIMS

1. A ceramic precursor composition used for manufacturing resorbable or partly resorbable high-strength bioelements, wherein the composition comprises at least one silicate with Ca as the main cation with a resorption rate less or equal to that of the bone in-growth rate, which at least one silicate acts as the main binding phase in the cured material, wherein the at least one Ca-silicate is present in an amount of 50 weight-% or more, the remainder, if any, is constituted by additives such as inert phase, and/or additives that make the cured material radiopaque.
2. The ceramic precursor composition according to claim 1, wherein the main binding phase(s) further comprises phosphates, carbonates, sulphates of calcium, and combinations thereof.
3. The ceramic precursor composition according to claim 1 or 2, wherein the main binding phase(s) comprises $3\text{CaO}\cdot\text{SiO}_2$.
4. The ceramic precursor composition according to any of the preceding claims, wherein it further comprises at least one second binding phase based on phosphates and/or sulphates in an amount of less than 20 weight-% of the main binding phase/phases.
5. The ceramic precursor composition according to any of the preceding claims, wherein the second binding phase comprises soluble glass, e.g. phosphorous-containing glass, apatite-based materials, preferably soluble CaH-phosphate.
6. The ceramic precursor composition according to any of the preceding claims, wherein it further comprises glass particles, fibres, whiskers and/or platelets of slowly dissolving inorganic or inert mineral phases, preferably a Ca-silicate-based mineral or Ca-silicate glass and highly radio-opaque oxides, preferably zirconium oxide.

7. The ceramic precursor composition according to claim 6, wherein said inorganic slowly dissolving or inert mineral phases are present in an amount of less than 20 weight-%.
- 5 8. The ceramic precursor composition according to any of the preceding claims, wherein it further comprises hydrated particles particles of the same or of similar phases as those used for the main binding phase in an amount less than 40 weight-%.
- 10 9. The ceramic precursor composition according to any of the preceding claims, wherein it further comprises a ceramic powder of Ca-aluminate type in an amount less than 40 weight-%.
- 15 10. The ceramic precursor composition according to any of the preceding claims, wherein it further comprises low amounts of a polyacrylic-based material, less than 8 weight-%.
- 20 11. A cured chemically bonded ceramic material for high-strength bioelements used as a resorbable or partly resorbable biomaterial having a compressive strength exceeding 100 MPa, wherein the material as the main binding phase comprises at least one silicate with Ca as the main cation with a resorption rate less or equal to that of the bone in-growth rate, wherein the at least one Ca-silicate is present in an amount more than 50 weight-%, the remainder, if any, is constituted by additives such as inert phase and/or additives that
25 make the material radiopaque.
12. The cured ceramic material according to claim 11, wherein the main binding phase(s) further comprises phosphates, carbonates, sulphates of calcium, and combinations thereof.
30
13. The cured ceramic material according to claim 11 or 12, wherein the main binding phase(s) comprises hydrates of $3\text{CaO}\cdot\text{SiO}_2$.

14. The cured ceramic material according to any of claims 11-13, wherein it comprises at least one second phase based on phosphates and/or sulphates in an amount of less than 20 weight-% of the main binding phase/phases.
- 5 15. The ceramic precursor composition according to claim 14, wherein the second binding phase comprises soluble glass, e.g. phosphorous-containing glass, apatite-based materials, preferably soluble CaH-phosphate.
- 10 16. The cured ceramic material according to any of claims 11-15, wherein it further comprises slowly dissolving inorganic or inert mineral phases, preferably a Ca-silicate-based mineral or Ca-silicate glass.
- 15 17. The cured ceramic material according to claim 16, wherein the inorganic slowly dissolving or inert mineral phases are present in the amount of less than 20 weight-%.
- 20 18. The cured ceramic material according to any of claims 11-17, wherein it further comprises a stable chemically bonded ceramic of Ca-aluminate hydrate type in an amount less than 40 weight-%.
- 25 19. The cured ceramic material according to any of claims 11-18, wherein the material also comprises low amounts of a polyacrylic-based material, less than 8 weight-%.
- 30 20. The cured ceramic material according to any of claims 11-19, wherein the pH of the material mixed with curing liquid changes during curing from higher than 11-12 to less than 10 in 60 minutes.
21. The cured ceramic material according to any of claims 11-20, wherein the material has a compressive strength within 24 hours of at least 40 MPa.
22. The cured ceramic material according to any of claims 11-21, wherein the material has a compressive strength exceeding 120 MPa after more than 7 days.

23. The cured ceramic material according to any of claims 11-22, wherein the material after more than 7 days after curing has a K_{IC} -value exceeding 0.5 MPam^{1/2}.
- 5
24. The cured ceramic material according to any of claims 11-23, wherein the material has a dimensional change of less than 0.3 linear %, and /or an expansion pressure during hardening and curing of less than 5 MPa.
- 10
25. The cured ceramic material according to any of claims 11-24, wherein the ceramic material, when inserted or injected into a body, has a slow disintegration rate in water and body liquid throughout the setting time, i.e. that > 95% of the inserted mass is intact after a setting time of 5 minutes.
- 15
26. The cured ceramic material according to any of claims 11-25, wherein more than 60 weight-% of the material, when inserted in a body, is dissolved within 3 years.
- 20
27. A medical implant comprising a non-cured ceramic precursor composition according to claim 1 and/or a cured ceramic material according to claim 11.
28. Use of a medical implant according to claim 27 as a carrier material for drug delivery.
- 25
29. Surface coated device or substrate selected from the group consisting of an artificial orthopedic device, a spinal implant, a joint implant, an attachment element, a bone nail, a bone screw, and a bone reinforcement plate, wherein it is coated with a non-cured ceramic precursor composition according to claim 1 and/or a cured ceramic material according to claim 11.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 2005/001304

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: A61L, A61K, C04B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 20040117030 A (NIKLAS AXEN ET AL), 17 June 2004 (17.06.2004), claims 1-2 --	1-29
A	US 20040043053 A (HYUN SEUNG YU ET AL), 4 March 2004 (04.03.2004) --	1-29
A	WO 2004058194 A1 (DOXA AKTIEBOLAG), 15 July 2004 (15.07.2004) --	1-29
A	FR 2843748 A1 (SEPTODONT OU SPECIALITES SEPTODONT SA), 27 February 2004 (27.02.2004) --	1-29

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search

7 December 2005

Date of mailing of the international search report

12-12-2005

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 2005/001304

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 19923956 A1 (ALBERT-LUDWIGS-UNIVERSITÄT FREIBURG), 30 November 2000 (30.11.2000) --	1-29
A	US 5840336 A (TSUNG-MIN HSU ET AL), 24 November 1998 (24.11.1998), column 4, line 46 - line 51, claim 1 -- -----	1-29

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2005/001304

INTERNATIONAL PATENT CLASSIFICATION (IPC):

A61L 27/10 (2006.01)

A61K 47/02 (2006.01)

A61L 27/58 (2006.01)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/SE 2005/001304

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